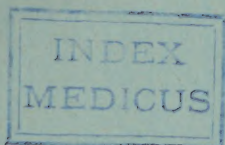


Prudden (T. M.)



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*An Experimental Study of Mycotic- or  
Malignant Ulcerative Endocarditis,*

FROM THE LABORATORY OF  
THE ALUMNI ASSOCIATION OF THE COLLEGE OF PHYSICIANS AND  
SURGEONS, NEW YORK.

BY

T. MITCHELL PRUDDEN, M. D.,

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It is convenient to group the inflammatory lesions of the endocardium into two classes—first, those in which the more prominent and constant character is the new formation of connective tissue, either in or upon the valves and general endocardium. This form of lesion may be designated by the name of *simple endocarditis*. Several varieties of this lesion may be recognized on the basis of their morphological characters. Thus the valves or the general endocardium may be simply thickened or sclerosed by a new formation of connective tissue, in a manner analogous to the interstitial production of new connective tissue so frequently seen in various internal organs. Or, either with or without a simple sclerosis, there may be irregular thickenings of, or distinct outgrowths from, the endocardium—most frequently on the valves—in the form of polypoid projections, irregular warty excrescences, etc.

The tissue composing these outgrowths may be dense and firm like cicatricial tissue, or more soft and cellular like granulations, or some of the various forms of young connective tissue. Between these two extremes there may be all intermediate forms, which doubtless represent different phases in the development of the new tissue.

These new growths are liable to ulcerate, to become calcified, to become covered with loosely or closely adherent thrombi, from which emboli—always simple and non-infectious—may be swept off into the bloodvessels, producing infarctions and other disturbances of the peripheral circulation. A local inflammatory reaction may express itself in the accumulation of leucocytes in and about the bases of these outgrowths or so-called vegetations.



In another, an acute variety of simple endocarditis, there may be no new formation of tissue, but the valves and endocardium may be simply swollen and succulent and covered with larger or smaller thrombi; or they may ulcerate and the surfaces of the ulcers may be covered with thrombi.

In contrast to these, for the most part primarily proliferative lesions, stands the second form of endocarditis, namely, the *malignant ulcerative* or *mycotic endocarditis*, in which the dominating morphological and biological factor is the presence of bacteria of one form or another, and the necrotic or ulcerative change which their presence induces. Add to these features the variable inflammatory reaction of the surrounding tissue—which is expressed by the more or less marked accumulation of leucocytes near the seat of necrosis, and the infectious nature of the emboli which are liable to form, and the main characters of the type of endocarditis which form the subject of the present paper, are sufficiently outlined.

The writer means by malignant ulcerative endocarditis a form of lesion always associated with some kind of bacteria. The causative relation of these bacteria to the lesions, and, consequently, the justification of the classification and nomenclature, are points upon which it is hoped that the results of the present investigation may throw some light. However much some of the varieties of simple endocarditis may resemble the mycotic, both clinically and in the gross appearance of the lesions—and the similarity is in some cases exceedingly and puzzlingly close—in view of our present knowledge they seem to be etiologically, and to a certain extent morphologically, entirely distinct. The similarity in the gross appearance is usually due to the more or less voluminous thrombi which may form over the surface of the lesions in both alike. There are cases presenting an acute clinical history in which we find upon the heart valves larger and smaller, more or less abundant vegetations, sometimes composed in part of new-formed or forming connective tissue and sometimes entirely of thrombi, now without ulceration, and again with a very extensive necrotic process involving large loss of substance and with or without embolism. These may be appropriately called cases of acute endocarditis, or acute ulcerative endocarditis when the necrotic tendencies prevail, but neither the primary nor the secondary lesions contain bacteria, nor, as a rule, does the more or less pronounced stamp of an acute infectious disease prevail, as it is apt to do in cases of malignant ulcerative endocarditis. But one of these forms of endocarditis may be superimposed upon the other, when both clinical and gross morphological features may be very difficult to interpret correctly. It is more especially some of the forms of simple chronic endocarditis upon which the malignant type may be superimposed, and thus may indeed, as it would seem, form one of the predisposing or

determining conditions without which the bacterial lesion would not be developed. This point will be considered more in detail further on. Finally, the possibility should be recognized that a proliferative change may occur secondary to the mycotic lesion, and thus bring about a certain degree of recovery.

The steps by which our knowledge of malignant endocarditis has grown are those common to most of the better understood acute infectious diseases. At first it was set aside from other apparently similar or related disorders by a set of clinical characters which were grouped under the general terms, malignant, septic, typhoid. The striking appearance of the heart valves, which presented soft and apparently rapidly formed and often very voluminous vegetations, with a tendency to local necrotic and multiple distant lesions—soon came to be regarded as characteristic of this form of disease. The growth of knowledge concerning embolism and thrombosis and their effects, to which the observations of Virchow so materially contributed, did much to explain both symptoms and lesions.

Very early in this, which may be called the morphological period in the history of this disease, certain very minute granules or corpuscles—masses of which were often seen to be surrounded by a homogeneous area—were detected in the cardiac as well as in the peripheral lesions.<sup>1</sup> These granules were sometimes simply described without speculation as to their nature, sometimes were pronounced, either conjecturally or positively, to be parasitic organisms. But neither the general knowledge upon the subject of microorganisms nor the technical facilities for their study were sufficiently advanced to give these earlier observations much more than an historical interest and importance.

Once turned in this direction, however, the tide of observation swept in numerous data, bearing more or less closely upon the relations of bacteria to this disease. In 1872 Hjalmar Heiberg<sup>3</sup> found microorganisms in a case of ulcerative endocarditis in puerperal fever, and his observations were confirmed by Virchow. Eberth<sup>4</sup> found them in a case of pyæmic endocarditis in the same year, while Virchow wrote at length upon them in an article on chlorosis and endocarditis puerperalis.<sup>5</sup>

In 1873 Eberth,<sup>6</sup> Wedel,<sup>7</sup> and Larzen<sup>8</sup> recorded new observations, and in 1874 cases were added by Eisenlohr,<sup>9</sup> Burkhart,<sup>10</sup> and Maier.<sup>11</sup> Certain granular bodies, which they were reserved in claiming positively to be microorganisms, were recorded by Lehman and van Deventer<sup>12</sup> in 1875. In the following year Gerber and Birch-Hirschfeld<sup>13</sup> described another case, drawing the analogy with a case of simple pyæmia, in which the general lesions were similar, but the heart lesion was absent.

The impetus of a dominant theory or a very peculiar concurrence of cases led Klebs<sup>14</sup> to the belief that all varieties of acute vegetative endocarditis were of mycotic nature, and, furthermore, that for the rheumatic



variety there was one form, and for the septic another form of bacteria. Koster<sup>15</sup> also regarded all acute endocarditis as of bacterial origin, and was led from his observations to the belief that it was due to emboli of the vessels of the valves and endocardium. Litten<sup>16</sup> was, also, of the opinion that all forms of acute endocarditis are of parasitic nature, and reports a number of cases.

At this time Hiller,<sup>17</sup> becoming alarmed at the rapidly accumulating data in favor of the bacterial origin of this disease, felt impelled to throw himself into the breach, and it is not a little curious to observe how many of the arguments which he used in his polemic against the probability of its bacterial origin are just those which most readily fall into line as confirmatory of the results of research at the present time. But steadily with the improvement of the technique of staining the bacteria and the increasing knowledge of their biological characters grew the record of new observations. From 1878–1879 new cases were recorded by Eichhorst,<sup>17</sup> Cayley,<sup>18</sup> Purser,<sup>19</sup> Mygind,<sup>25</sup> and Hamburg.<sup>21</sup> The latter observer examined fourteen cases of acute endocarditis, and found cocci in but four of them. These four cases were all ulcerative, and three were in puerperal fever and one in pyæmia. He found no bacteria in several other ulcerative cases.

At this time Winge<sup>2</sup> formulated, for the first time, a consistent theory of this disease, based largely upon a carefully observed case, assuming the transportation of microbes from external wounds through the veins to the heart, where, he conjectured, they produced the lesions by lodgement upon the valves. Overbeck,<sup>22</sup> in 1881, reports the examination of five cases of ulcerative endocarditis, in all of which were numerous hemorrhages in various organs. In four of these cases micrococci were present, in one they were absent. In the first four cases there were numerous abscesses of the internal organs. In all of these cases there were old endocarditic lesions. Bramwell,<sup>27</sup> in eleven cases of ulcerative endocarditis examined, found micrococci in all.

The writer has for some time been examining the cases of endocarditis which came into his hands—particularly those with an acute history—for the presence of bacteria. The method of staining at first employed was the simple fuchsin staining and decolorization with alcohol. Since its announcement, Gram's method has been used in all cases, and controlled by the simple fuchsin method, as before. The whole number of cases examined was twenty. Of these, seven were of simple chronic verrucous endocarditis; thirteen were cases of ulcerative endocarditis, with a history of acute illness.

*Chronic vegetative endocarditis*, seven cases. In none of these were bacteria found, either by staining or by culture methods.

*Acute ulcerative endocarditis*, thirteen cases. In four of these cases the ulcerations, though well marked, were not extensive, and the throm-

basis was insignificant in amount. In the remaining nine cases there were extensive ulceration and local thrombosis. In five of these thirteen cases sphæro-bacteria were present in large numbers. In the remaining eight cases they were entirely absent. In four of these thirteen cases cultures were made, one (recorded below) with positive, the others with a negative result. The cases in which a negative result was obtained by the culture methods gave also negative results in the morphological examination. The bacteria were, in all cases, of small spheroidal form, and were morphologically identical. The ulceration and thrombus formations were quite as extensive in the series of cases in which the bacteria were absent as in those in which they were present.

1. *Cases in which bacteria were absent.* In seven of these eight cases there was old thickening of the valves of the left side of the heart. The ulcerations were on the mitral alone in four cases, and on the aortic cusps in four. There was simple infarction of the spleen in two cases, enlargement and softening of the spleen in three. In three cases there was a well-defined previous history of acute articular rheumatism; in five there was no previous history at all. In one case there was purulent meningitis with acute general bronchitis, and in one acute lobar pneumonia.

2. *Cases in which bacteria were present.* In four of these five cases there was old thickening of the valves and endocardium. The mitral alone was affected in two cases; the aortic alone in one; the tricuspid in one; and both mitral and tricuspid in one. The spleen was large and soft in all of the five cases, and there were fresh and old infarctions in four. In two cases there was no previous history, but there was old thickening of the aortic and mitral valves; in one case there was acute articular rheumatism; in two cases pyæmia. In one of the two pyæmic cases—which both resulted from injury—there was malignant osteomyelitis and periostitis, purulent pericarditis, and thrombosis of the pulmonary artery; while in the other there were multiple abscesses in the brain and kidney, infarctions of liver and spleen, and abscess of the myocardium.

It does not enter into the scope of the present paper to detail the clinical history of these cases, but it may be remarked that the two classes of cases—*i. e.*, those with and those without bacteria—ran courses nearly equal in acuteness and rapidity, and presented symptoms equally obscure.

While in the great majority of cases the bacteria found in the lesions of malignant ulcerative endocarditis are all of the small spheroidal form, a few cases are recorded in which bacilli were present. Such a case is mentioned by Osler,<sup>23</sup> one is reported by Smith and Northrup,<sup>24</sup> and one by Netter and Martha.<sup>25</sup> Cornil<sup>26</sup> mentions the occurrence of bacillus tuberculosis in the vegetations in a case of phthisis, as do also



Rindfleisch and Kundrat. All of these scattered observations rest, however, upon a purely morphological basis, and bearing in mind how readily the bacilli of decomposition may make their appearance in this situation, if the examination be delayed or the manipulations faulty, our estimate of the significance of the presence of bacilli in a very few cases should be held in abeyance until more detailed and careful observations are at hand.

We now enter upon a new phase in the story of investigations upon this disease. Hitherto the studies recorded have been simply morphological, and the conclusions regarding the significance of the presence of bacteria have been largely conjectural. The very large number of observations coincident in result have made it certain that sphaero-bacteria are very constant factors in certain, but not in all cases of ulcerative endocarditis; but whether they are of etiological importance or only insignificant concomitants, does not yet appear.

In a rather crude way attempts have, indeed, for some time been made to supplement our knowledge of the morphology of these lesions by experiments bearing upon the pathogenic characters of the bacteria so frequently present.

As early as 1870, Winge<sup>2</sup> made subcutaneous inoculations of animals with particles of the vegetations, but without definite results. In 1872, Heiberg<sup>3</sup> made peritoneal and intravenous inoculations, also without positive results. Panophthalmitis and keratitis have been produced in the rabbit by direct inoculation by Eberth,<sup>6</sup> Birch-Hirschfeld,<sup>13</sup> and Osler.<sup>23</sup> Grancher<sup>28</sup> made some cultures of bacteria from a case of ulcerative endocarditis after rheumatism, but their characters were not sufficiently carefully studied for identification, and they died before inoculations were practised. Perret and Rodet<sup>29</sup> report without sufficient detail some inoculations of dogs with vegetations from a case of acute endocarditis rubbed up with filtered water, and state that vegetations were found upon the valves. They also state that they used fluid cultures with equal success. The account, however, is so lacking in detail and the experiments in precision that one can hardly attach much importance to them, especially as dogs are liable to spontaneous acute endocarditis. But these experiments are all crude and belong to an earlier epoch of research.

The necessity of obtaining pure cultures of bacteria of suspected pathogenic nature and the study of their biological as well as their morphological characters and their effects upon animals, are now recognized as imperative for the solution of such problems as that which now engages us. The use of solid culture media, and particularly the use of gelatine or other form of plate cultures as elaborated by Koch, has placed in our hands the means of isolating such of the bacteria



of disease at least as are "facultative" saprophytes and capable of developing and growing in the culture media at present known to us.

A series of cultivation and inoculation experiments made by Hare,<sup>27</sup> and recorded in a recent number of this journal, gave negative results. Unfortunately, the bacteria, which were cultivated from the kidney abscesses of one of Bramwell's cases, in gelatine bouillon tubes and on potato appear to have become contaminated and were neither identified nor fully described. It does not appear from the text that the gelatine plate method of Koch was resorted to for separating and identifying the bacteria presumably derived from the heart lesion, and without this such a series of experiments could hardly be expected to yield permanently valuable results.

Impressed with the importance of the biological method of research, Wyssokowitsch,<sup>30</sup> under Orth's direction, recently instituted a series of experiments which led to unexpected and positive results. He started with the fact recorded by Ottomar Rosenbach<sup>31</sup> in 1878, namely, that a traumatic injury to the heart valve of the rabbit by means of a sound introduced through the carotid is not followed by an inflammatory reaction, and by no or but a very slight thrombosis.\* Then choosing, somewhat at random, the well-known pathogenic organisms, the significant relations of which to pyæmia and the suppuration process have been so thoroughly studied, namely, *Streptococcus pyogenes*, he introduced pure cultures of these into the vein of the ear of the rabbit, soon after having produced the injury to the heart valves as above described. The seven rabbits operated upon died in from one to eleven days—at the latter period when a very small quantity of the inoculating material was used. In five of these animals numerous larger and smaller vegetations were found near and in some cases somewhat distant from the seat of injury, both where the valve was perforated and where the sound had evidently touched the endocardium. These vegetations consisted of large numbers of sphaero-bacteria similar to those injected, a little fibrin, and red blood-cells. Beneath these was a distinct necrotic area, which grew larger as the bacteria made their way into the tissue from the surface. In some cases there were pericarditis and cardiac abscesses. Metastases in the kidneys, spleen, and knee-joint were noted. Suppuration around the bacterial masses was not observed. In one case in which the injection

\* These results of Rosenbach's experiments, showing the comparative tolerance of the endocardium toward mechanical interference, recall a notion, formerly widely entertained, that the endocardium was an exceedingly sensitive structure; and in the early days of the accumulation of knowledge concerning pyæmia it was held by some that the chills were produced by the irritating effect upon the endocardium of the entrance of pus into the heart.

Bichat recommended in cases of asphyxia to stir up the heart by passing a sound down a vein of the neck and tickling the endocardium. This was actually done by Dieffenbach in cases of Asiatic cholera with collapse, but without effect. Virchow found, however, by introducing into the heart glass sounds, pieces of ice, meat, etc., that the endocardium was quite insensitive. Virchow, *Gesammte Abhandlungen*, p. 229.

of the bacteria was delayed for forty-eight hours, no such changes in the endocardium were observed. In the other case the operation was unsuccessful, and the experiment vitiated by the chance introduction of some contaminating bacteria of another species.

After these striking results, Wyssokowitsch repeated the experiments, using for inoculation cultures of the bacteria so frequently associated with the streptococcus in pyæmia and the suppurative process, namely, *Staphylococcus pyogenes aureus*. Three rabbits were inoculated after the preliminary operation: two with a concentrated and one with a much diluted emulsion of the bacteria. The first two died on the first and second days and presented lesions in general similar to those induced by the streptococcus, except that the bacteria were not so abundant and not in such large masses in the lesions, and the suppurative process near their seat of deposit was well marked. The third rabbit died thirty-eight days after the operation, and presented no lesions, except the original puncture of the valve. Following this one rabbit was operated on in the same way, and immediately inoculated with the coccus sepsis of Nicolaier. It died on the fourth day, and the results were essentially the same as with the streptococcus. A local infection of one side of the left auricle, which was in contact across the cavity of the auricle, with a vegetation evidently the result of the extension of the process from the injured valve through the heart wall, gave an excellent example of the extension of the process *per continuatatem* as well as *per contactum*.

The original results of Rosenbach were confirmed by operations on four rabbits. Two rabbits were inoculated after the operation on the valves with micrococcus tetragenous and two with the bacillus pneumoniae of Friedländer, but with entirely negative results.

Finally, Wyssokowitsch succeeded in obtaining pure cultures of bacteria from a fresh case of malignant ulcerative endocarditis in man with metastatic lesions. Those obtained by the usual plate culture method presented all the characters of *Staphylococcus pyogenes aureus*. Cultures from this case gave, by a repetition of the above operation, results identical with those obtained in the use of the same species from another source.

Shortly after the announcement of these results by Wyssokowitsch, Weichselbaum<sup>32</sup> published the results of his examinations of three cases of malignant ulcerative endocarditis, and one case of acute vegetative endocarditis. The three cases of ulcerative disease were young females, two with rheumatism and one with a history of old valvular lesions. In one of these cases he found and cultivated for identification from the pericardial fluid, the cardiac vegetations, spleen and urine, a mixture of *Staphylococcus pyogenes aureus* and *albus*, and *Streptococcus pyogenes*. In another case he cultivated from the vegetations *Streptococcus pyogenes*, while in the third case he identified only the *Staphylococcus*



*pyogenes aureus*. In the case of acute vegetative endocarditis, which was that of a young rheumatic female, he identified *Streptococcus pyogenes* only. His experiments on animals, of which the details are not yet published, gave, he states, results essentially identical with those of Wyssokowitsch.

While the work of Wyssokowitsch and Weichselbaum was going on and especially after their results were announced, Ribbert<sup>22</sup> was studying the subject with a somewhat different technique. He omitted the preliminary direct mechanical injury to the endocardium, and introduced potato cultures of *Staphylococcus pyogenes aureus* directly into the veins of rabbits. At first he scraped off the superficial growth of the culture with a little of the potato, and ground them fine before the injection; his results in this way were inconstant. When, however, he injected with the bacteria larger particles of the potato among and into which they had grown—particles as large as would pass the canula of the injecting syringe—and used quite large quantities, he was able to produce not only cardiac abscesses and areas of necrosis in the myocardium, but most marked vegetations upon the endocardium, especially on the mitral and tricuspid valves. The vegetations were most apt to be at the points of attachment of the chordæ tendinæ to the valves, and on the outer surface of the valves; they were never found on the aortic and pulmonary valves.

Microscopical examination showed the various stages in the development of the endocardial lesion. At first there was a simple lodgement of the bacteria upon the surface of the endocardium—in a few cases a particle of potato was found on the surface with the bacteria clustered around it. The bacteria gradually penetrated the underlying tissue, causing a local necrosis over which the thrombus formed. For the details of the microscopical study we must refer to the original. In a word, Ribbert obtained essentially the same results as Wyssokowitsch and Weichselbaum by introducing with the bacteria a foreign substance, which apparently either produced the necessary mechanical injury or brought about the adherence of the bacteria to the endocardial surfaces. By his method of experimentation, however, it is necessary to use larger quantities of the inoculating material, a proceeding which is always undesirable when conclusions, bearing upon similar lesions in man, are to be drawn from the results.

Ziegler<sup>23</sup> identified the sphæro-bacteria in one case of malignant ulcerative endocarditis as *Staphylococcus pyogenes aureus*.

Striking and momentous as are the results of the just recounted experiments, it is obviously of the highest importance that they should be repeated under varying conditions, and that the sphæro-bacteria now so frequently found in ulcerative endocarditis in man by the improved methods of staining, should be more precisely identified and in every

suitable case studied by the methods which the solid culture media of Koch have placed in our hands.

The primary purpose of the writer in the experiments now to be recorded, was to repeat independently and from the beginning the experiments of Wyssokowitch in so far as they could be done with the fully identified bacteria derived from a case of human malignant ulcerative endocarditis.

All of the bacteria used in these studies were derived from a case for the organs and history of which the writer is indebted to the courtesy of Dr. George M. Swift, of New York.

Mary C., aged fourteen years. Had convulsions at eighteen months, scarlatina early in life but no rheumatism, and was apparently well and strong. She was admitted to hospital February 22, 1886, for operation on clubfoot. Cuneiform osteotomy was performed "antiseptically" on February 26, and for the first few days patient did well but complained of pain in the foot. On March 6, there was an erysipelatous redness about the wound and the temperature rose, but was reduced by antipyrin. She became delirious at times and unconscious; had twitching of muscles on left side, and died on March 10.

*Autopsy.* *Brain:* Meninges apparently normal, ventricles not dilated. Numerous small sub-pial hemorrhages, mostly quite superficial, on cerebral convolutions. A few hemorrhages were at the bottom of the sulci, and some of these involved small areas of the gray matter, which about them was soft and red. *Heart:* Pericardium normal. Aortic and pulmonary valves normal. Scattered along the edges of the tricuspid and mitral valves and nearly completely investing them, were irregular rows of larger and smaller, white and red, firm and closely adherent excrescences, some of them covered with loosely hanging red and white thrombi. On one of the papillary muscles of the left ventricle was a small eroded area loosely covered with a thin red fibrinous pellicle. In the left ventricle were also numerous small subendothelial petechie and one small abscess. *Lungs* normal. *Spleen* soft and large, and presented an irregular grayish friable area about one centimetre in diameter. *Kidneys* moderately large, capsule free, studded with numerous small yellowish-white spots surrounded by zones of diffuse redness. On section, the cortices were thickened, light in color, markings obscure. Everywhere, both in cortex and medulla, the cut surface was thickly besprinkled with small yellowish-white spots and streaks. The spots were from one to three millimetres in diameter and many of them were surrounded by a sharp red zone. There were also numerous sharply circumscribed red spots. *Liver* presented several larger and smaller white irregular areas, some of them very soft, having the appearance of infarctions. Other organs appeared normal.

*Microscopic examination.* The tricuspid and mitral valves are irregularly thickened, the new tissue being mostly dense and firm, and consisting largely of basement substance. In the superficial portion, however, the cells are more abundant and fusiform, stellate, and spheroidal. The surfaces of these—for the most part apparently old vegetations—are irregularly bestrewn with larger and smaller masses of very small spheroidal bacteria arranged in pairs or in large or small irregular clusters,



or lying singly. They stain readily by Gram's or by the simple fuchsin method. These bacterial masses are in part covered—in part intermingled with granular matter, a few leucocytes, fibrin, and a few red blood-cells. Beneath the mass of bacteria there is in most cases a larger or smaller area of necrosis of the vegetation in which the nuclei remain unstained, and the basement substance presents a translucent, finely granular, or structureless appearance. In many places there is an irregular zone around the areas of dead tissue in which there is a greater or less accumulation of leucocytes. In general, the necrotic process in this case is not advanced, involving only little spots here and there on the surface of the vegetations where the tiny masses of bacteria have found lodgement.

The lesions of the other internal organs were those common to pyæmic abscesses and infarctions.

The kidney presented microscopically a variety of phases in its lesions corresponding to the varied gross appearance. In some places the larger, but particularly the smaller bloodvessels were plugged by masses of bacteria with little or no reaction of the tissue about them. In other places the bacterial masses were surrounded by a zone of dilated bloodvessels. Again, there was localized necrosis around the bacterial plug, while around this necrotic area there was sometimes simply a zone of enlarged bloodvessels, or an accumulation of leucocytes, or both. In some cases the bacterial mass was closely surrounded by an accumulation of leucocytes, so dense that the kidney tissue for some distance around was entirely concealed, or completely broken down. The liver and spleen presented the usual effects of infectious emboli. The brain showed microscopically a plugging of the smaller bloodvessels in the hemorrhagic areas with bacteria, while around these plugs were either a simple zone of dilated bloodvessels, or extravasation, or a localized breaking down of brain tissue; or, in a few cases, an extravasation of blood surrounded by a zone of purulent infiltration. Finally, in some places, the brain tissue surrounding the bacterial embolus appeared to be simply necrotic, without hemorrhage, and without inflammatory reaction.

Some portions of the kidney were placed in a covered sterilized jar, and allowed to stand at the temperature of the room for twenty-four to sixty-six hours. Stained sections made at various intervals from carefully removed fragments of these pieces showed, in the most evident manner, a large and steady increase in the number of bacteria. The bacteria, furthermore, were no longer, as in the freshly hardened tissue, mostly confined to the bloodvessels and the abscess, but were in the lumina of the tubules and outside of the vessels in the cavities of the glomeruli. This increase in the number of pathogenic bacteria in the tissues after death,<sup>35</sup> which is now a well-established fact, is too often overlooked, and should always be taken into consideration, not only in estimating the number of bacteria present in any given case, but also in determining the positions which they occupy.

The organs were received in a very fresh condition, and with a most strict adherence to the usual antiseptic precautions, several peptonized gelatine plate cultures were prepared in varying degrees of dilution from the vegetations of the valves and from several of the renal abscesses. At the ordinary temperature of the laboratory at the end of the second day numerous colonies were just visible to the naked eye. Under a low mag-

nifying power these colonies presented sharp edges, were moderately finely granular, of a slightly brownish color, and had just begun to liquefy the gelatine around them. No other forms of colonies appeared in the plate, except an occasional aerial surface contamination. From these plate colonies, gelatine, agar, and blood-serum tubes and potatoes were inoculated. In gelatine tubes the culture medium became gradually fluid with a whitish pellicle on the surface, which gradually assumed a light yellow color, and soon sank to the bottom. The liquefaction progressed until the entire mass was fluid, and as this went on the gelatine itself became darker in color, and the bacterial sediment of a deeper yellow. On agar the growth in the thermostat at 37° C. was rapid, spreading usually from the line of inoculation for from one to three millimetres over the surface, and growing less vigorously along the puncture line. The surface growth, at first white, gradually assumed a more or less bright yellow color, particularly in the older parts. Along the puncture line the growth remained white. The agar was not liquefied, and the yellow color became more intense as the culture grew older, finally deepening to a rich orange. On blood-serum a yellow pellicle formed without fluidification. On potato the growth was slow at chamber-temperature, gradually assuming a light or deep yellow color. The gelatine and agar cultures were transplanted through many generations, their characters remaining unchanged.

Six rabbits were inoculated subcutaneously with about two cubic millimetres of an agar culture. Five of these developed abscesses which contained the same bacteria. The sixth rabbit presented no reaction. Injection of about the same quantity of the culture mixed with sterilized three-quarter per cent. salt solution into the pleural and abdominal cavities of three rabbits, were followed by a rise of temperature of from one to three degrees on the two following days and after this there was complete recovery.

It will be seen from this *résumé* of the characters of the bacteria cultivated from the heart vegetations, and from the renal abscesses in a case of malignant ulcerative endocarditis in man, that they were the *Staphylococcus pyogenes aureus*, which is so frequently associated with pyæmia and the suppurative process.<sup>36</sup> This, it will be remembered, is the same species which Wyssokowitsch found in his one case, Weichselbaum in two of his four cases, and Ziegler in one case of this disease.

An unlooked-for confirmation of the pathogenic properties of these bacteria occurred in the person of one of the writer's associates in the laboratory. He was inoculated in the finger from handling the abdominal viscera of one of the rabbits dead on the second day after an intravenous injection of a pure culture. He suffered for several days from a severe phlegmon of the finger, with great tenderness of the lymphatic glands of the entire body. On opening the abscess of the finger which rapidly developed, about one drachm of pus was discharged, from which with the greatest ease the same *Staphylococcus pyogenes aureus* was cultivated.



ANIMAL EXPERIMENTS.—These were performed exclusively on rabbits.

*Punctures of the valve without subsequent inoculation.* At first five rabbits were operated on by Rosenbach's method, for the sake of control, as follows:

The animal being narcotized or anesthetized was stretched on the Czernak table with the neck raised by a block of wood so as to straighten the carotid as much as possible. The hair was removed over the right carotid region and the skin thereabouts carefully cleansed with sublimate solution 1:1000. The carotid was now exposed for an inch of its course, and two ligatures passed around it about three-quarters of an inch apart. The distal ligature was drawn tight and tied, while the proximal was left loose. A V-shaped opening being now made with scissors in the carotid, a small silver probe, carefully sterilized by heat, was passed into the vessel and by a little manipulation carried downward. When the semilunar valves were reached a slight resistance was observed. This was readily overcome by a moderate pressure on the probe which readily punctured one of the cusps. At this moment the heart usually bounded and its beats became irregular and very rapid. On the withdrawal of the probe the proximal ligature was tied, the wound washed thoroughly with sublimate solution, closed by sutures, and bandaged with absorbent cotton and flannel. A blowing sound could in most cases be distinctly heard after the valve puncture, and the heart beats remain for a few hours frequent but regular.

Very little blood was lost in these operations and the animal rapidly recovered spirits and appetite. The wound healed in all cases by first intention, when the animals were allowed to live long enough, and on killing them at periods of from twenty hours to thirty-six days, no marked reaction was found at the seat of puncture of the valves or in the internal organs. The edge of the somewhat ragged opening in the valve was in one case loosely covered by a filmy clot. After a few days the edges of the puncture became smooth and slightly thickened, and so remained up to the latest period at which the animals were killed, namely, thirty-six days.

*Conclusions.* Simple puncture of a cusp of the aortic valve in rabbits with a sterilized probe introduced under antiseptic precautions through the carotids, is followed by no result other than a slight thickening of the edge of the puncture through the valve.

*Punctures of the valve followed by inoculation.* Following the method of Wyssokowitsch, eight large, healthy rabbits were operated on in the manner just described, and after from one to three hours a varying quantity of the cultures of the *Staphylococcus pyogenes aureus* from the above case of malignant ulcerative endocarditis was introduced by means of a sterilized Koch's balloon inoculating syringe into the vein of the ear. For this purpose not less than one cubic centimetre of a fluidified gelatine culture, or from one to two cubic millimetres of an agar culture was used, mixed with a small quantity of three-quarter per cent. salt solution.

One of these rabbits died in sixteen hours, and showed a broad scratch at the lower end of the carotid, and a simple puncture of one of the cusps of the aortic valve. There was congestion of the lungs, but no other lesion. In one other animal the temperature rose to  $104\frac{3}{8}^{\circ}$  on the second day, and the animal seemed dull and ill, but on the third day the animal appeared well, and continued so until the twenty-sixth day, when it was killed. There was a simple puncture of the valve with slightly thickened edges and numerous calcareous deposits in the kidney, but no other lesions.

The operation on the remaining six animals gave positive results, which were so nearly similar that they may be summarized as follows: The temperature rose from  $103\frac{1}{2}^{\circ}$  to  $105^{\circ}$  during the first few hours, and usually continued elevated until within a few hours of death, when it fell to normal or below. The animals, for the most part, refused food, appeared stupid, and disinclined to move, and toward the end grew very weak, and scarcely able to sit upright. A feeble convulsive movement of the entire body frequently immediately preceded the death, which occurred, on the average, in from forty to fifty-five hours.

In all cases the wound in the neck was dry and healing favorably. In four cases there was sero-fibrinous pericarditis, and the exudation contained numerous sphero-bacteria, which morphologically and by culture were identified as *Staphylococcus pyogenes aureus*. In four of the six cases a cusp of the aortic valve was punctured, while in these and in the two others there was a line of roughening along the lower end of the carotid and on the endocardium below the valves in the line of passage of the probe. It will thus be seen that in two of the six positive cases the probe had slipped between the valves, injuring the endocardium below and the aorta above.

In all of the six cases, along the line of carotid erosion, around the seat of puncture, or on the surface of the injured valves, and on the endocardium below, were larger and smaller, irregular elevated masses, resembling fresh cardiac vegetations.

On microscopical examination these vegetations were found to consist of masses of sphero-bacteria, intermingled with fibrin, granular matter, and a few red and white blood-cells. The larger of these vegetations rested on a more or less evidently eroded endocardial surface.

The microscopical examination of the endocardium and inner surface of the carotid near the points of contact of the probe, and sometimes for some distance from it, revealed tiny elevations of similar character, but so small as to be scarcely, or not at all, visible to the naked eye. Among these smaller elevations could be traced all intermediate forms between the simple deposit of a tiny cluster of bacteria on the surface of the endocardium, and well-marked vegetations, in which the bacteria were intermingled with fibrin and granular material, and rested on a necrotic



base. The localized necrosis of tissue in the immediate vicinity of the clusters of bacteria, both large and small, was a very marked feature in all of these experimental cases. In many cases, not only the fibrin around the bacterial masses, but the endothelium and subendothelial tissue, to a varying depth, were converted into a structureless or finely granular material, which did not stain.

In one case there was a moderate proliferation of the endothelium at the outer border of the necrotic area, and in many, especially when the life of the animal was prolonged, there was a zone of small spheroidal cells at a short distance from the necrotic region in the subendothelial tissue.

In one case the heart muscle was thickly beset with tiny abscesses, some of which projected beneath the endocardium. In two other cases, one and two small subendocardial abscesses were found. Microscopically these abscesses consisted of pus cells and fragments of necrotic muscle fibre which had lost their striation, while bacteria were found either within the abscess, or at a short distance from its border, and blood-vessels could be readily demonstrated the lumina of which were completely plugged with them. The very early period after inoculation—sometimes within thirty hours—at which these abscesses may be fully formed, is worthy of note.

The right auricle and ventricle in most of these cases were distended with voluminous loose red clots in which numerous bacteria had lodged. These were identified as the same species as those inoculated.

The lungs were, as a rule, normal, as was also the liver, but in one case the latter organ presented a large infarction involving the anterior border.

The spleen was uniformly enlarged, frequently to twice or thrice its normal size, and soft. It contained the same bacteria.

The kidneys were congested and in all but one of the six cases presented several large infarctions. In one case they were studded with larger and smaller abscesses.

The microscopical examination of the kidney revealed most exquisite forms of pyæmic abscesses and infarctions. Larger and smaller blood-vessels were plugged with masses of sphero-bacteria, in some cases with no alteration of tissue around them. Or, directly surrounding the bacterial mass there would be a larger or smaller area of necrosis; while these necrotic areas were in turn, in many cases, enclosed by a wide or narrow zone of purulent infiltration. The origin of the infarctions could in many cases be most readily demonstrated in the plugging of larger vessels by enormous masses of bacteria. Partial or nearly complete injection of the vascular tufts of the glomeruli with bacteria was of frequent occurrence.

In one case there was a gangrenous area of about one inch in diameter

in the large intestine. The only brain lesion noticed was a moderate congestion in three cases.

In the above mentioned case of this series, in which the animal was at first ill, but afterward recovered, and was killed on the twenty-sixth day, the kidneys were thickly beset with larger or smaller calcareous masses, mostly elongated and more or less contorted. These encroached upon the kidney tissue in their vicinity, which was thickly infiltrated with small spheroidal and elongated cells, and were apparently the result of recovery from the original renal emboli.

In all of these cases gelatine plate cultures were made from the heart and kidney lesions, and the pure cultures thus obtained were used in continuing the inoculations from one animal to another. It was from one of the later cultures in the series that the above mentioned human inoculation occurred. Thus the bacteria, which so promptly produced the severe phlegmon of the finger, originating, so far as these experiments go, in the heart valves of a case of human malignant ulcerative endocarditis, had passed successively through three rabbits, producing death in each case, and through almost innumerable generations in the culture tubes and plates.

*Conclusions.* This series of experiments shows, in confirmation of the results obtained by Wyssokowitsch, that the introduction into the blood of rabbits of a considerable quantity of a pure culture of *Staphylococcus pyogenes aureus*, after a mechanical injury to the endocardium, is capable of producing, in addition to the peripheral changes characteristic of pyæmia, the typical lesions of malignant ulcerative endocarditis, and that the seat of these cardiac lesions is determined by the position and extent of the mechanical injury to the endocardium.

*Chemical injury to the endocardium followed by inoculation.* In order to ascertain the effects of chemical irritants in rendering the endocardium vulnerable to the action of the bacteria, I have varied the preliminary operation by arming the point of the probe with a fused mixture of equal parts of silver and potassium nitrate, covering this with a thin coating of sugar and passing it down the right jugular vein. The point of the probe may be brought to any desired position, after a little practice, before the sugar dissolves, and thus the mitigated caustic may be rubbed against the endocardium, the parts above having been protected by the film of sugar. The point of the probe may be held against the wall of the right auricle, or carried between the leaflets of the tricuspid valve, or pushed down into the ventricle. A small, firmly adherent thrombus usually, but not always, forms at the points of contact of the silver salt with the endocardium and into this thrombus the bacteria make their way, or in its absence lodge on the endocardium and induce lesions similar to those above described as following a mechanical endocardial injury. Hemorrhages and abscesses of the lungs are more fre-



quent after these operations on the right heart, but otherwise the peripheral lesions are the same as those above described. Seven rabbits were operated on in this way with identical results.

*Conclusions.* The action of chemical agents upon the endocardium in the rabbit produces a condition of predisposition to the lodgement and growth of *Staphylococcus pyogenes aureus* similar to that induced by a simple mechanical injury.

For the purpose of control, two rabbits were operated on by passing a sterilized probe down the jugular into the right heart, allowing it to remain there for a few seconds and then withdrawing it and closing the wound. After this, on introducing the usual dose of *Staphylococcus pyogenes aureus* culture into the blood through the ear vein the animals died with renal infarctions and swollen spleen, but there were no heart lesions.

*Chemical injury to the endocardium not followed by inoculation.* In three rabbits, the sterilized probe armed with silver nitrate was introduced into the heart through the jugular and its point rubbed against the tricuspid valves and endocardium until the silver salt was dissolved. It was then withdrawn and the wound closed. These animals remained apparently well and were killed, one in twenty minutes, one in five, and the other in six days. In the animal killed after five days there was a slight loose red and white clot adherent to the edges of the tricuspid valve. In the other animals there was no clot and no apparent change in the endocardium. Microscopical examination of the clot showed no bacteria.

*Conclusions.* These control jugular experiments show that a simple light contact of a sterilized probe with the endocardium of the right heart does not, in rabbits, produce a sufficient injury to that structure to determine a localization of *Staphylococcus pyogenes aureus* in the heart after a subsequent intravenous injection of them; furthermore, that a simple chemical injury to the endocardium, such as is produced by the contact of silver nitrate, not followed by bacterial inoculation, does not, in rabbits, produce the lesions of endocarditis.

**SUMMARY.**—Bacteria are frequent in a certain proportion of cases of acute ulcerative endocarditis in the cardiac, and, when these exist, in the peripheral lesions. These bacteria are small and of spheroidal form in almost all of the cases thus far described; but in a few cases the presence of bacilli has been noted. There are cases of ulcerative endocarditis with extensive destruction of tissue and large formation of thrombi, in which the lesions are entirely free from bacteria. In these cases, as a rule, the endocardium is the seat of an old inflammatory process and the peripheral embolisms, infarctions, etc., do not contain bacteria.

In many cases of acute ulcerative endocarditis associated with bacteria the valves and endocardium are also the seat of old inflammation.

The destructive process and formation of thrombi in the heart valve and endocardium may be as marked and extensive in the cases in which the bacteria are absent as in those in which they are present; but in the latter class of cases the embolic lesions which are apt to be developed are of an infectious nature, and the general course of the disease is apt to bear the stamp of an acute infectious disorder.

These two classes of cases may be appropriately designated as *ulcerative* or *acute ulcerative endocarditis*, but those in which the bacteria are present should be distinguished by the term *malignant bacterial* or *mycotic ulcerative endocarditis*.

The gross appearance of the valvular lesion does not always or usually enable us to distinguish between these two forms of disease. Bacteria are sometimes present in cases of acute vegetative endocarditis, but in the lesions of chronic proliferative endocarditis they do not appear to occur at all.

The bacteria which are present in the cardiac and peripheral lesions in cases of malignant ulcerative endocarditis are the causative factors in the disease. This has been shown by three independent observers, who have isolated the same species of bacteria from cases of this disease in man; obtained them in quantity in pure cultures; induced in rabbits by their inoculation, under special conditions, lesions of the endocardium as nearly identical with those in man as the nature of animal experimentation will permit; and finally determined the presence of the same bacteria in the cardiac and peripheral lesions of the operated animals.

The bacteria apparently produce the cardiac lesions by lodgement on the surface of the valves and endocardium, when the latter are rendered vulnerable to their action either by mechanical or chemical injury; or by the presence of old inflammatory alterations; or by conditions unknown to us.

Bacterial embolism of bloodvessels of the heart valves is apparently not of frequent occurrence, as was formerly believed.

The only bacteria which have been thus far absolutely identified as occurring in the lesions of malignant ulcerative endocarditis in man are *Streptococcus pyogenes* and *Staphylococcus pyogenes aureus*. This identification has been made in six cases.

It has been demonstrated that other species of bacteria than those above mentioned are capable of causing similar lesions in rabbits under similar experimental conditions.

REMARKS.—The relations of malignant ulcerative endocarditis to the acute diseases such as pneumonia,\* typhoid fever, etc., in connection with

\* Some recently recorded experiments by Netter on ulcerative endocarditis associated with acute lobar pneumonia (*Archives de Physiologie normale et path.*, Aug. 15, 1886, p. 106) contain interesting and important data. But the meagreness of detail in the record of his experimental work, the uncer-



which it is apt to occur, still remain obscure, and in the light of the new methods are almost entirely unstudied. It is, however, noteworthy that in all the cases of this disease thus far fully studied by biological methods, the bacteria identified are those which play so important a rôle in pyæmia and the inflammatory processes in general. In these cases the disease may be regarded as one of the local lesions of pyæmia.

The great frequency with which the acute ulcerative disease is engrafted upon an old endocardial lesion would seem to indicate that in the human subject the absence of endothelium, or the roughness of the surface of the thickened endocardium, affords conditions of predisposition for the lodgement, and vulnerability toward the incursions of the bacteria, where once they gain access to the blood, similar to those produced experimentally in the rabbit by mechanical or chemical means.

To seek for the nature of the acquired vulnerability in a diminished vitality of the endothelial cells whereby they become unable to cope successfully with the ptomaine-producing bacteria which find lodgement upon or near them, would lead us in a direction toward which many experimental data point; but it is perhaps better, for the present, to remain on what seems to be fully established ground. The injection of *Staphylococcus pyogenes aureus* into the blood of the rabbit may cause death by pyæmia, but it does not induce malignant ulcerative endocarditis. Simple chemical or mechanical injury to the valves and endocardium does not induce endocarditis. Perform both operations at once and the disease almost invariably follows.

This predisposing factor in disease, which has long been recognized, has become more evident and demanded a more precise comprehension since the causative relationship of microorganisms to certain diseases has been established. In the disease before us, the gross nature at least of the predisposing factor is very simple and evident. In other diseases—tuberculosis or pneumonia, for example—the conditions are much more subtle and difficult of definition but none the less important.

In the search after these predisposing conditions in diseases already proven to be immediately due to the action of bacteria, such a vast amount of labor remains to be performed, both in the clinical, physiological, and morphological departments, that it becomes evident that the whole field is by no means won, as is too often assumed, when a disease is demonstrated to be of bacterial origin.

The immediate duty of observers of malignant ulcerative endocarditis from the etiological standpoint is evidently to study every suitable case completely by the biological as well as the morphological methods and thus ascertain the exact characters of the bacteria involved.

tainty which still exists as to the significance of the various so-called pneumococci, and the far-reaching deductions which he makes from experimental procedures by no means free from grave technical errors, seem to render unnecessary at present a more extended consideration of his paper.

Finally, in view of the significant relationship of the bacteria of pyæmia and suppuration to malignant ulcerative endocarditis in the cases thus far fully examined, it is evident that a demonstrably diseased condition of the heart valves, or a previous history which would suggest the possibility of such a condition, should be an additional incentive to the practice of a vigilant antiseptic in operations, however simple, upon this class of cases.

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